Chapter 9

Latency of Bovine Herpesvirus 1 (BoHV-1) in Sensory Neurons

Clinton Jones

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Abstract

Bovine herpesvirus 1 (BoHV-1) is an important pathogen of cattle and cofactor for bovine respiratory disease, a polymicrobial disease. Acute infection of cattle leads to abundant expression of lytic cycle viral genes, high levels of virus shedding, and clinical symptoms. Following acute infection, lifelong latency is established in sensory neurons. Only the latency-related (LR) gene locus, which encodes at least two microRNAs and several proteins, is abundantly expressed in latently infected neurons. Increased corticosteroids, due to external stressors, disrupt the maintenance of latency and increase the incidence of reactivation from latency, which is crucial for virus transmission. For example, calves latently infected with BoHV-1 consistently reactivate from latency following a single intravenous (IV) injection of the synthetic corticosteroid dexamethasone. In contrast to wild-type BoHV-1, an LR-mutant virus that has three in-frame stop codons at the amino terminus of the first open reading frame in the LR gene (ORF2) does not reactivate from latency following dexamethasone treatment. The ability of dexamethasone to initiate BoHV-1 reactivation from latency in calves makes it an attractive model to identify early events that occur during reactivation from latency. Viral and cellular factors that regulate the BoHV-1 latency-reactivation cycle are discussed in this review.

Keywords: bovine herpesvirus 1, latency, sensory neurons, stress-induced reactivation, glucocorticoid receptor, Wnt signaling pathway, pioneer transcription factors

1. Introduction

Bovine herpesvirus 1 (BoHV-1) is a large double-stranded DNA virus that causes significant economical losses to the cattle industry. Acute infection is typically initiated in mucosal

epithelium and leads to high levels of virus shedding. Infection of cattle with BoHV-1 can lead to conjunctivitis, pneumonia, genital disorders, abortions, and bovine respiratory disease complex (BRDC), a life-threatening upper respiratory tract infection, reviewed in [1, 2]. In spite of high levels of viral replication, cellular and humoral immune responses eventually clear the virus.

Like other Alphaherpesvirinae subfamily members, BoHV-1 establishes lifelong latency in ganglionic neurons within the peripheral nervous system [3]. The latency-reactivation cycle can be operationally divided into three distinct phases: (1) establishment, (2) maintenance, and (3) reactivation from latency. In contrast to acute infections where all viral genes are abundantly expressed, the latency-related (LR) gene is the only viral transcript abundantly expressed in sensory neurons within trigeminal ganglia (TG) of latently infected calves during the maintenance of latency [4–6]. LR-RNA is antisense with respect to the bICP0 gene [7, 8], which encodes a major viral transcriptional trans-activator. The LR gene encodes at least two micro-RNAs and more than one protein. These proteins and micro-RNAs are detected in a subset of latently infected neurons [9–11] implying that they regulate certain aspects of the latency-reactivation cycle. LR protein expression is necessary for the latency-reactivation cycle [12]. The synthetic corticosteroid dexamethasone (DEX) consistently induces reactivation from latency in calves or rabbits, reviewed in [1, 2]. Reactivation from latency initiated by DEX reduces LR gene products, which correlates with the induction of lytic cycle viral genes. The ability of BoHV-1 to reactivate from latency is crucial for viral transmission and complicates designing effective modified live vaccines.

BoHV-1 is an attractive model to examine the latency-reactivation cycle of Alphaherpesvirinae subfamily members because reactivation from latency can be consistently induced in calves. Consequently, early events during reactivation from latency can be identified and characterized. In contrast to mouse models used to examine events that control the herpes simplex virus 1 (HSV-1) latency-reactivation cycle, the powerful genetic approaches available in mice are lacking in cattle. In this review, the pathogenic properties of BoHV-1 and details of the latency-reactivation cycle are discussed.

2. Pathogenesis of BoHV-1

2.1. Clinical disease caused by BoHV-1

Three BoHV-1 subtypes have been described: BoHV-1.1 (1), BHV-1.2a (2a), and BHV-1.2b (2b) [13]. Subtype 1 strains are frequently found in cattle located in North America, Europe, and South America. Infection with Subtype 1 isolates can result in infectious bovine rhinotracheitis (IBR) and can be detected in the upper respiratory tract. In addition, Subtype 1 isolates are frequently detected in aborted fetuses suggesting that infection caused the abortion. Subtype 2a can also cause IBR and abortions [14] as well as genital infections that can lead to infectious pustular vulvovaginitis (IPV) or balanopostitis (IBP), reviewed in (2). Subtype 2a strains of BoHV-1 are frequently detected in Brazil and Europe prior to the 1970s

(14). Subtype 2b strains, in general, are less pathogenic than Subtype 1 and frequently detected in Australia and Europe [15]. Subtype 2b strains can be detected in cases of respiratory disease and IPV/IPB, but not in aborted fetuses [14, 16].

In breeding cattle, abortions and genital infections are relatively common. Genital infections occur in bulls (IPB) and cows (IPV) within 1–3 days after mating or close contact with infected animals. Initial clinical signs following genital infection of cows are mild vaginal infection and frequent urination [17]. Lesions are routinely observed on the penis and prepuce in bulls. Inflammation of the uterus and transient infertility with purulent vaginal discharge may persist for several weeks if secondary bacterial infections occur. Transmission, in the absence of visible lesions, can occur following artificial insemination with semen from a bull subclinically infected. Abortions can occur at the same time as respiratory disease, but may also occur up to 100 days after infection, which is presumably due to reactivation from latency.

2.2. BoHV-1 is a cofactor of bovine respiratory disease complex

With respect to feedlot cattle, the respiratory form of BoHV-1 is the most common disease observed and is usually caused by Subtype 1 strains. BoHV-1 is an important cofactor of BRDC [18, 19], a polymicrobial disease initiated by stress as well as virus infection. Increased susceptibility to secondary bacterial infections correlates with depressed cell-mediated immunity after BoHV-1 infection [20–23]. Mucosal surfaces of the upper respiratory tract, which promotes the establishment of *Mannheimia haemolytica (MH)* in the lower respiratory tract, are compromised by BoHV-1 infection [24–26]. Productive infection increases neutrophil adhesion and activation [27], which can also amplify the effects of *MH. MH* is a gram-negative bacterium [28] that exists as normal flora in the upper respiratory tract of healthy ruminants [29]. This commensal relationship is disrupted following stress or coinfections [30], and then *MH* is the predominant organism that causes bronchopneumonia [24–26, 31]. BoHV-1 also stimulates inflammasome formation [32], which may contribute to BRDC by enhancing inflammation in the lung.

BoHV-1 interferes with immune responses by several mechanisms. For example, CD8+ T-cell recognition of infected cells is impaired by repressing the expression of major histocompatibility complex class I (MHC I) and transporter associated with antigen presentation [33–35]. The gN orthologs encoded by pseudorabies virus (PRV) and BoHV-1 inhibit transporter-associated antigen processing (TAP)-mediated transport of cytosolic peptides into the endoplasmic reticulum, which then interferes with the assembly of peptide-containing ternary MHC-I complexes in vitro in virus-infected cells [36, 37]. gN also targets the TAP complex for proteosomal degradation [36]. CD4+ T-cell function is impaired during acute infection of calves because BoHV-1 infects CD4+ T cells and induces apoptosis [1].

Stimulation of beta-interferon (IFN-β)-dependent transcription is an immediate-early response following virus infection that does not require de novo protein synthesis [38–43]. Activation of existing transcription factors by protein kinases stimulates IFN-β transcription. In contrast to humans or mice, cattle contain three IFN-β genes regulated by distinct promoters [44, 45]. BoHV-1 infection of primary bovine cells inhibits expression of all three

bovine IFN-β genes [46]. Blocking viral protein expression by cycloheximide, a protein synthesis inhibitor, prevents BoHV-1 from suppressing IFN-β responses [46]. In contrast to primary bovine cells, BoHV-1 infection of established bovine kidney cells strongly induces IFN-β3 RNA expression [46]. Two viral regulatory proteins, bovine-infected cell protein 0 (bICP0) [47–49] and bICP27 [50], interfere with IFN-β-promoter activation. The bICP0 protein induces the degradation of a transcription factor, interferon-regulatory factor 3 (IRF3), which is necessary for IFN-β-promoter activation [47]. In addition, bICP0 interacts with interferon-regulatory factor 7 (IRF7), another transcription factor that stimulates IFN-β-promoter activity [49]. bICP0 also induces the degradation of the promyelocytic leukemia protein (PML) [51], a crucial component of an intrinsic antiviral complex localized to the nucleus [52–54].

3. Vaccines directed against BoHV-1

Several commercially available BoHV-1 vaccines are available and can be divided into two categories: modified live attenuated virus (MLV) or killed whole virus [55].

Most MLVs were developed more than 30 years ago by serial passage in tissue culture. MLVs generally induce humoral and cellular immune responses as a result of virus replication. The MLVs establish latency and upon reactivation from latency can readily be transmitted to pregnant cows and cause abortions [56]. One study demonstrated that vaccination with a common MLV reduced the number of live births relative to no vaccination [57]. MLVs can also be pathogenic in small calves because their immune system is not fully developed, and most MLVs are immunosuppressive. Recently, there has been an increase in IBR outbreaks in vaccinated feedlot cattle, which is likely due to vaccine outbreaks [58, 59]. A number of vaccine and virulent field strains were sequenced and important differences identified between the respective strains [60]. Consequently, polymerase chain reaction (PCR) primers are available that allow one to identify MLV strains versus virulent field strains. This knowledge will make it possible to identify vaccine strains, or emerging BoHV-1 strains not protected by existing MLVs that lead to the break.

Killed whole virus vaccines are usually produced by chemical treatments: for example, formaldehyde, β-propiolactone, or binary ethyleneimine. Killed vaccines are safe but typically require more than one injection to achieve acceptable neutralizing antibody levels and do not always induce cellular immune responses. With respect to formaldehyde-inactivated killed vaccines, antigens may also be denatured, which can affect the immunogenicity of vaccine preparations. Killed vaccines also require suitable adjuvant formulations and adjuvants can induce injection-site reactions. Better adjuvants may improve the efficacy while reducing the number of vaccinations necessary to achieve good protection in cattle. In summary, better vaccines that do not cause abortions or reactivate from latency need to be developed.

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4. Transition from acute infection to establishment of latency: latency-related gene products promote latency

4.1. Productive infection

Acute infection of calves induces programmed cell death, inflammation, and high levels of virus shedding [1, 2, 32]. Viral gene expression during productive infection occurs in three distinct phases: immediate early (IE), early (E), or late (L). IE transcription unit 1 (IEtu1) encodes two crucial viral regulatory proteins, bICP0 and bICP4, which activate viral gene expression and DNA replication [61–63] (**Figure 1A**). IEtu2 encodes bICP22 [62]. A viral tegument protein, VP16 (also known as bTIF), is a viral structural protein present in the tegument that specifically trans-activates IE promoters. VP16 interacts with two cellular proteins (Oct1 and HCF-1) and this complex binds specific sequences in IE promoters [64, 65]. E genes, in general, encode nonstructural proteins that promote viral DNA replication. L genes encode proteins that comprise infectious virus particles.

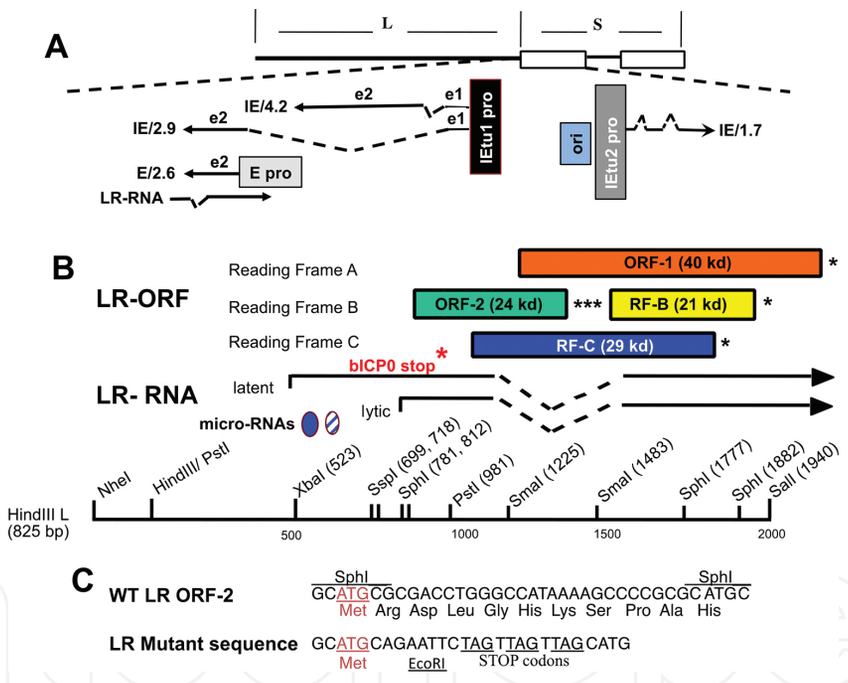

Figure 1. Schematic of BoHV-1 genes encompassing the LR gene. Panel A. Positions of IE transcripts and the LR transcript (LR-RNA) are presented [62, 63, 161]. The bICP4 protein is translated from the IE/4.2 transcript. The bICP0 protein is translated from the IE/2.9 transcript. The IEtu1promoter activates the expression of IE/4.2 and IE/2.9, and is denoted by the black rectangle (IEtu1 pro). The bICP0 protein can also be translated from an early transcript designated as E/2.6 because exon 2 (e2) contains all of the protein-coding sequences. An early promoter (E pro) drives the expression of the E/2.6 transcript. The origin of replication (ORI) separates IEtu1 from IEtu2. The IEtu2 promoter (IEtu2 pro) drives the expression of the bICP22 protein. Solid lines in the transcript position map represent exons (e1, e2, or e3) and dashed lines denote introns. The viral origin of replication (ori) is located near IETu2 promoter. **Panel B**. Partial restriction map of the LR gene. The LR gene contains two open reading frames (ORF-1 and ORF-2) [4]. Reading frame B (RF-B) and RF-C do not contain a methionine at the beginning of the open reading frame. The asterisks denote the position of stop codons that are in frame with the respective open reading frame. **Panel C**. Wild-type sequences near the N-terminus of ORFS compared to that in the LR mutant virus [12, 73].

4.2. Sensory neurons are the primary site for establishing latency

Cell-to-cell viral transmission leads to viral entry into sensory neurons. Following a burst of viral gene expression, lytic cycle viral gene expression is subsequently extinguished. If infection is initiated within the oral, nasal, or ocular cavity, the primary site for latency is sensory neurons in trigeminal ganglia. Lytic cycle viral gene expression [66] and infectious virus [12] are detected in TG from 2 to 6 days after infection. In contrast to infection of mucosal epithelial cells, significant numbers of infected neurons survive and these surviving neurons harbor intact viral genomes. This phase is operationally defined as the establishment of latency. Periodically, reactivation from latency occurs, virus is shed from peripheral sites, and consequently BoHV-1 is widespread in cattle [1, 7, 8, 67]. Other types of neurons may be latently infected; however, this has not been explored. Lymphocytes that reside in the tonsil and circulating blood have been reported to contain viral genomes when collected from latently infected calves [68].

4.3. The BoHV-1 latency-related gene locus is abundantly expressed in infected TG neurons and encodes several products

The LR gene is the only locus in the viral genome abundantly expressed in latently infected neurons [4, 6–8, 67, 69]. LR-RNA has unique start sites in TG and is antisense and overlaps the bICP0 gene, suggesting that it inhibits bICP0 expression [9, 70] (**Figure 1B**). The LR gene has two well-defined open reading frames (ORF1 and ORF2), and two reading frames that lack an initiating methionine (RF-B and RF-C). Two micro-RNAs encoded by the LR gene are abundantly expressed in latently infected neurons and they reduce bICP0 protein expression, but not ICP0 RNA levels in transient transfection studies [11]. The micro-RNAs have different predicted binding sites on bICP0 mRNA suggesting that they cooperate to reduce bICP0 protein levels. A small ORF located downstream from bICP0 (ORF-E) is expressed in latently infected TG neurons [71] and induces neurite formation in mouse neuroblastoma cells [72], suggesting that ORF-E regulates certain aspects of the latency-reactivation cycle.

An LR-mutant virus that contains three stop codons at the N-terminus of ORF2 was constructed and analyzed (see **Figure 1C** for location of stop codons). Following infection of calves, the LR-mutant virus exhibits diminished clinical symptoms during acute infection, and reduced virus shedding from the eye, TG, or tonsils [12, 73, 74]. Although the LR-mutant virus grows like wild-type BoHV-1 and the LR-rescued virus in cultured bovine cells, it expresses LR-RNA earlier than wild-type (wt) virus and stimulates a stronger interferon response in cultured cells and tonsils of acutely infected calves [75]. ORF1 and ORF2 expression are not detected in TG neurons during latency following infection with the LR-mutant virus [10, 76]. Wt BoHV-1, but not the LR-mutant virus, efficiently establishes latency and consistently reactivates from latency following a single injection of the synthetic corticosteroid DEX [12]. Although the LR-mutant virus grow less efficiently compared to wild-type BoHV-1 in TG [73], the LR mutant induces higher levels of apoptosis in TG during establishment of latency [77]. ORF2, in the absence of other viral genes, can inhibit apoptosis in Neuro-2A cells [78] suggesting that ORF2 has important roles during the latency-reactivation cycle.

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ORF2 is a 181-amino acid protein that has little or no amino acid similarity to known proteins. The protein localizes to the periphery of the nucleus in transfected Neuro-2A cells and contains a functional nuclear localization signal. When the nuclear localization signal is deleted, ORF2 localizes to the plasma membrane of transfected Neuro-2A cells. Neuro-2A cells were used for these studies because ORF2 protein expression is consistently detected; conversely, other common cell lines that can be readily transfected do not support ORF2 expression. ORF2 preferentially interacts with single-stranded DNA; however, alanine substitution of threonine or serine residues in consensus protein kinase A (PKA) or protein kinase C (PKC) phosphorylation sites generates a protein that preferentially interacts with double-stranded DNA [81]. ORF2 does not appear to specifically bind to DNA sequences or interact with RNA. ORF2 stability is regulated by C-terminal sequences and PKA/PKC phosphorylation sites [79, 82].

ORF2 or an ORF2 isoform interacts with three cellular transcription factors (Notch1, Notch3, and c/EBP-alpha) [83, 84]. Since c/EBP-alpha stimulates IEtu1 promoter activity [85] and Notch 1 can slightly stimulate productive infection and certain viral promoters [83], ORF2 may promote the establishment of latency by interfering with lytic cycle viral gene expression. ORF2 amino acid sequences that interfere with Notch functions do not overlap ORF2 sequences necessary for inhibiting apoptosis [80], suggesting that these functions are separable. The ability of ORF2 to interfere with Notch functions stimulates the differentiation of Neuro-2A cells into differentiated neuronal-like cells, as judged by neurite sprouting [79, 82, 86]. It is well established that Notch family members inhibit differentiation of neural progenitor cells [87–91], suggesting that ORF2 helps infected neurons recover from infection and promotes normal neuronal functions. In summary, ORF2, ORF-E, and two micro-RNAs encoded by the LR gene possess properties that are predicted to enhance the establishment of latency.

5. Maintenance of latency

5.1. LR gene products are likely to promote maintenance of latency

Maintenance of latency lasts for the life of the host. Hallmarks of maintaining latency include the following: (1) infectious virus is not detected by standard virus isolation procedures, (2) abundant expression of lytic cycle viral genes does not occur, and (3) LR gene products are abundantly expressed in latently infected sensory neurons. The most obvious difference between maintenance versus establishment of latency is the initial burst of lytic cycle viral gene expression that occurs following infection of sensory neurons, and is extinguished during the establishment of latency.

Herpes simplex virus 1 latency-associated transcript (LAT), such as the LR gene, is abundantly expressed during latency and was reported to promote the maintenance of latency, reviewed in [7, 67, 92]. A recent study concluded that LAT maintains a pool of latently infected neurons that have the potential to reactivate from latency [93]. A cellular micro-RNA that interferes with the expression of the HSV-1 regulatory protein (ICP0) [94] and a cellular transcription factor (ATF3) [95] that enhances LAT expression are proposed to support the maintenance of

latency. LR gene products, in particular the ability of both micro-RNAs to inhibit bICP0 expression, are candidates to suppress lytic cycle viral gene expression during maintenance of latency. The ability of ORF2 and ORF-E to stimulate neurite formation may help latently infected neurons retain their differentiated phenotype and normal functions.

5.2. Potential roles of cellular genes during maintenance of latency

Our recent studies demonstrated that a cellular transcription factor, β-catenin, is readily detected in latently infected TG neurons, but not in TG neurons from uninfected calves. Nearly all β-catenin+ neurons are also ORF2+; however, β-catenin+ neurons do not express the lytic cycle viral regulatory protein (bICP0) suggesting that ORF2 regulates β-catenin expression. During the course of reactivation from latency, the number of β-catenin+ neurons decreases significantly, which correlates with the induction of two Wnt antagonists, dickkopf-1 (DKK-1) and secreted frizzled-related protein 2 (SFRP2).

Wnt is a family of secreted glycoproteins that interacts with frizzled and the coreceptor LRP5/LRP6, reviewed in [96]. In the absence of the Wnt ligand or when a Wnt antagonist is expressed at high levels, a β-catenin destruction complex forms in the cytoplasm (**Figure 2A**). This complex (axin, adenomatous polyposis gene (APC), GSK3β, and CKIα) hyper-phosphorylates β-catenin: consequently, β-catenin is polyubiquitinated and degraded by the proteasome.

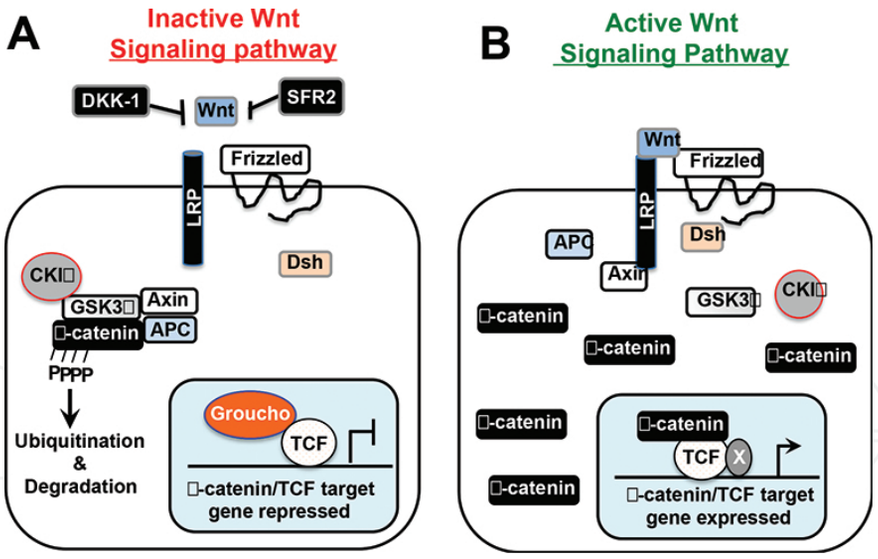

Figure 2. Schematic of canonical Wnt signaling pathway. Panel A: Key regulators of inactive Wnt pathway. In the absence of Wnt ligand, a β-catenin destruction complex, Axin, APC (adenomatous polyposis gene), GSK3β, and CKIa hyper-phosphorylate β-catenin, which leads to ubiqutination and degradation. Soluble frizzled-like proteins (DKK-1 and FRP2) prevent Wnt binding to its true receptors. In the absence of active Wnt signaling, TCF bound to DNA interacts with transcriptional repressors and transcription is repressed. **Panel B: Key regulators of active Wnt pathway**. Binding of Wnt to LRP and frizzled family members disrupts the β-catenin destruction complex and hypo-phosphorylated β-catenin accumulates in the nucleus. Nuclear β-catenin binds TCF family members, displaces repressors of TCF-dependent transcription, and recruits additional transcriptional regulators (denoted by X) resulting in transcriptional activation.

Wnt binding to its receptor disrupts the β-catenin destruction complex (**Figure 2B**). Consequently, the transcription factor β-catenin is stabilized, enters the nucleus, and interacts with TCF (T-cell factor) family members bound to the consensus site AGATCAAGG. β-catenin binding to TCF displaces bound corepressors (e.g., Groucho) and recruits coactivators (denoted as X) to activate Wnt target genes.

β-catenin activation regulates navigation of axons to their synaptic targets and stimulates axonal growth, reviewed in [97–101]. Several lines of evidence have concluded that disrupting the Wnt signaling pathway stimulates neurodegeneration, reviewed in [97, 98, 102]. Wnt signaling via β-catenin activation also inhibits apoptosis in several cell types [103–105], including neurons [106]. Chronic stress or increased corticosteroids induce a secreted Wnt antagonist, dickkopf-1 (DKK-1), which stimulates neuronal damage in the hippocampus [107], and ischemic neuronal death [108]. DKK-1 also mediates glucocorticoid-induced changes in human neuronal progenitor cell growth and differentiation [109]. Secreted frizzled-related protein 2 SFRP2 may also stimulate neuronal survival because it induces cell death in the developing hindbrain [110]. The ability of LR gene products, ORF2, for example, to stabilize β-catenin protein levels may promote maintenance of latency [103].

6. Reactivation from latency

6.1. Activation of viral gene expression during reactivation from latency

BoHV-1 reactivation from latency is consistently initiated by the synthetic corticosteroid DEX [6–8, 12, 67, 111], suggesting that DEX flips a molecular switch that disrupts the maintenance of latency (see **Figure 3** for schematic of putative steps leading to reactivation from latency). Within 6 h after DEX treatment, LR gene products are nearly undetectable in TG [6, 11, 82], lytic cycle viral RNA expression is detected in TG neurons of latently infected calves [68, 112], and apoptosis of T cells persisting in TG can be detected [112]. CD8+ T cells also persist in TG of humans or mice latently infected with HSV-1 [113–119] and have been reported to promote maintenance of latency [120, 121–124]. CD8*α* dendritic cells have also been reported to regulate the HSV-1 latency-reactivation cycle using mouse models of infection [125]. CD8+ T cells and/or CD8*α* dendritic cells may be important regulators of the BoHV-1 latency-reactivation cycle.

Two viral regulatory proteins, bICP0 and VP16, are expressed in the same neuron within 90 min after DEX treatment of latently infected calves; conversely, two other late proteins (gC and gD) are not readily detected until 6 h after DEX treatment [105, 126]. Fewer neurons express gC or gD relative to bICP0 or VP16. The fact that VP16 is a late gene implies that a novel mechanism induces VP16 expression very soon after DEX administration. However, the VP16 promoter is not activated by DEX or any of the DEX-induced transcription in transient transfection assays [127, 128]. With respect to HSV-1, VP16 has been proposed to be an important factor during initial stages of reactivation [129, 130]. Nearly all bICP0+ and VP16+ neurons express the glucocorticoid receptor (GR) suggesting that GR+ latently infected neurons are more likely to reactivate. The IEtu1 promoter that drives bICP0 and bICP4 (two

crucial viral transcriptional regulators; **Figure 1A**) expression is stimulated by DEX and contains a consensus GR-binding site bound by the activated GR [128]. Inspection of the BoHV-1 genome revealed that more than 100 GR-binding sites are present, suggesting that additional viral promoters are stimulated by corticosteroids during reactivation from latency.

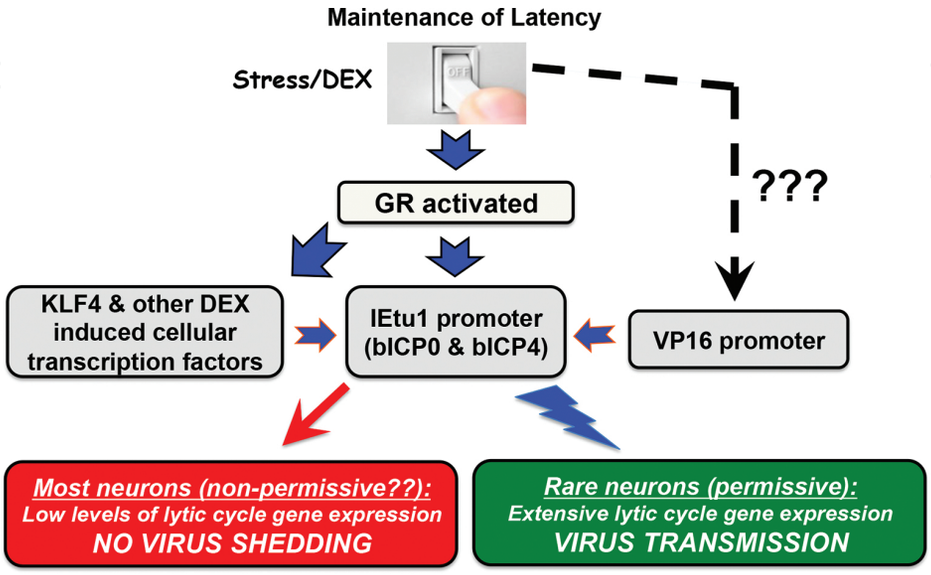

Figure 3. Putative steps leading to reactivation from latency. Stress, as mimicked by the synthetic corticosteroid dexamethasone (DEX), is a molecular switch that is predicted to stimulate viral gene expression via activation of the GR- and DEX-induced transcription factors. The IEtu1 is a crucial promoter that appears to be stimulated during the early stages of reactivation from latency. The mechanism by which VP16 expression is stimulated is not known. Many latently infected neurons lack cellular factors and are unable to support virus production and consequently reestablish latency. A small subset of latently infected neurons possesses the necessary factors to support extensive lytic cycle viral gene and production of infectious virus. The fate of these neurons is unclear.

6.2. Regulation of cellular gene expression in TG neurons during early phases of DEX-induced reactivation from latency

Within 3 h after DEX treatment, Pentraxin 3, a regulator of innate immunity and neurodegeneration [131], and two cellular transcription factors, promyelocytic leukemia zinc finger (PLZF) and Slug, are induced at least 15-fold in TG [127]. Additional DEX-induced cellular transcription factors were also identified in TG: Sam-pointed domain Ets transcription factor (SPDEF) and three Kruppel-like transcription factors (KLF), KLF4, KLF6, and KLF15. Immunohistochemistry studies confirmed that these cellular transcription factors are expressed in TG neurons during early stages of DEX-induced reactivation from latency. In general, overexpression of a DEX-induced cellular transcription factor stimulated productive infection and certain viral promoters, including IEtu1and the bICP0 early promoter.

The finding that four KLF family members (KLF4, KLF6, KLF15, and PLZF) are stimulated during DEX-induced reactivation from latency is significant because KLF family members resemble the SP1 transcription factor family and both families of transcription factors interact with GC-rich motifs, reviewed in [132, 133]. In general, genomes of Alphaherpesvirinae

subfamily members, including BoHV-1 and HSV-1, are GC rich and many viral promoters contain Sp1 consensus-binding sites and additional GC-rich motifs [132]. KLF15 stimulates HSV-1 ICP0 promoter activity more than 400-fold, but not the HSV-1 VP16 and ICP4 promoters [134]. KLF4, SPDEF, and Slug also stimulate ICP0 promoter activity at least 100-fold. These transcription factors are induced in mouse TG neurons following explant and addition of DEX generally enhanced their expression. These studies provide evidence that KLF transcription factors stimulate BoHV-1 and HSV-1 transcription, which may consequently enhance productive infection and reactivation from latency.

Lytic cycle viral gene expression is not readily detected during the maintenance of latency because HSV-1 and presumably BoHV-1 genome exist as "silent" chromatin during latency, reviewed by [135–137]. In contrast to many transcription factors, the activated GR can specifically bind silent chromatin [138–140], generate a nuclease-hypersensitive site, and then promote initiation of transcription [141–142]. Activated GR only binds a subset of GREs in silent chromatin [143–144] and thus fits the criteria for being a "pioneer transcription factor," reviewed in [145, 146]. Purified KLF4, a DEX-induced transcription factor in TG neurons [127, 134], is also a pioneer transcription factor [145, 146] that can bind nucleosomes in vitro and preferentially targets silent sites enriched for nucleosomes in vivo [147]. We suggest that these two pioneer transcription factors (GR and KLF4) have the potential to convert a silent BoHV-1 genome into a transcriptionally active genome that subsequently expresses abundant levels of lytic cycle viral genes and produces infectious viral particles.

There appears to be a bottleneck with respect to completion of successful reactivation (production of an infectious virus particle). Many latently infected neurons apparently do not support extensive lytic cycle viral transcription and/or cellular factors necessary to produce an infectious viral particle that are missing or not expressed in sufficient quantities. These neurons are operationally defined as nonpermissive. Evidence for the existence of nonpermissive neurons comes from three studies: (1) few neurons express late proteins (gC and gD) relative to neurons that express VP16 and bICP0 [126], (2) only a small subset of latently infected sensory neurons produce infectious viral particles [6], and (3) the LR mutant does not reactivate from latency following DEX treatment even though the viral genome and LR-RNA are detected in TG during latency [12]. Many nonpermissive neurons are predicted to survive a stressful stimulus and reestablish latency. It is unclear whether a permissive neuron that reactivates from latency and sheds infectious virus can survive and reestablish latency. In a mouse model of HSV-1, neurons that support reactivation in vivo do not appear to survive [148].

7. Conclusions and unresolved questions

The latency-reactivation cycle of Alphaherpesvirinae subfamily members, including BoHV-1, is regulated by a complex series of virus-host interactions. Furthermore, BoHV-1 and cattle have evolved with each other making it difficult to model the latency-reactivation cycle in small animal models or cultured neurons. The HSV-1 LAT and BoHV-1 LR gene encode at

least three common functions crucial for the latency-reactivation cycle: (1) inhibit apoptosis [78, 149–152], (2) interfere with productive infection [11, 152, 153], and (3) promote sprouting of neurites in mouse neuroblastoma cells [79, 82, 154], which is predicted to promote neuronal repair and restore normal neuronal functions following infection. Although the LR gene restores wt levels of reactivation to an HSV-1 LAT null mutant [155] and ORF2 plays a role in this process [156], LAT does not appear to encode a protein. Thus, LAT-encoded microRNAs and other small noncoding RNAs are proposed to regulate the latency-related cycle.

A brief discussion of several unresolved questions is presented as follows:

- Is it necessary for viral DNA replication to occur in a latently infected sensory neuron that produces an infectious virus particle? Although it is clear that viral DNA replication must occur at peripheral sites for virus transmission or recurrent disease to occur during a reactivation episode, published reports that have directly tested whether viral DNA replication occurs in neurons during reactivation from latency are lacking. From a minimalist's standpoint, it would seem to be advantageous for the viral genome to merely express sufficient levels of viral proteins necessary to package the viral genome such that cell-to-cell transmission will occur. Considering that sensory neurons do not enter the cell cycle and replicate their chromosomes, there must be ingrained epigenetic signals that prevent the expression of cellular proteins necessary for DNA replication.
- What is the threshold of stress that leads to successful reactivation from latency? Mammals face stressful stimuli everyday but reactivation from latency (at least episodes that lead to virus shedding) does not occur every day. For successful reactivation episodes (one that leads to virus shedding from peripheral sites), there must be a relatively intense stimulus or a prolonged stimulus.
- Do neurons that produce infectious virus particles survive and reestablish a latent infection? As mentioned above, latently infected neurons yielding infectious virus particles probably do not survive in a mouse model of HSV-1 infection [148]. However, this study needs to be confirmed.
- Do other Alphaherpesvirinae subfamily members utilize similar pathways for regulating the latency-reactivation cycle as BoHV-1? HSV-1 does not reactivate as consistently as BoHV-1 following DEX treatment, suggesting that the GR is not as important. However, it should be noted that increased "stress" correlates with a higher incidence of reactivation from latency in humans [157–159]. DEX also stimulates reactivation from latency in TG neuronal cultures prepared from latently infected mice [114] and TG organ cultures latently infected with HSV-1 [160]. Although the exact mechanism is not likely the same, common pathways may flip a switch that initiates reactivation from latency.

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Author details

Clinton Jones

Address all correspondence to: clint.jones10@okstate.edu

Department of Veterinary Pathobiology, Center for Veterinary Health Sciences, Oklahoma State University, Stillwater, Oklahoma, USA

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